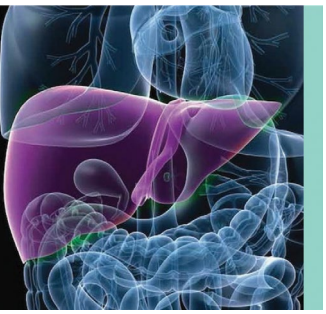

Historical Aspects of Ascites and the Hepatorenal Syndrome

Florence Wong, M.B.B.S., M.D., F.R.C.P.C., and Laurence Blendis, M.B.B.S., M.D., F.R.C.P.C.

Florence Wong.

Laurence Blendis.

Abbreviations: AKI, acute kidney injury; HRS, hepatorenal syndrome; IAC, International Ascites Club; ICA, International Club of Ascites; MELD, Model for End-Stage Liver Disease; sCr, serum creatinine; TIPS, transjugular intrahepatic portosystemic stent shunt.

From the Department of Medicine, Division of Gastroenterology, University of Toronto, Toronto, ON Canada.

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ASCITES

The Early Days of Paracentesis

Ascites or abdominal dropsy has been known since antiquity, according to descriptions in The Papyrus Ebers from the reign of Amenophis I in 1550 BCE in Ancient Egypt[1] and the Atharva Veda (from 1500-1300 BCE), in the Indian Subcontinent, in which *Jalodara*, the dropsy, is mentioned.[2] In the Old Testament, abdominal swelling was the divine punishment for a wife's adultery (somehow, but not unexpectedly, not for a man's adultery), but whether this swelling was due to ascites is not explained.[3] Arguably the most graphic portrayal of ascites was found among the excavations of pre-Hispanic Mesoamerica, from the Classic period (300–900 CE) of the Mayan civilization (Fig. 1).[4] As with many other terms in our medical lexicon, *ascites*, *dropsy*, and *paracentesis* all derived originally from Ancient Greek. Hippocrates the Koan (460-370 BCE)* recognized hydrops, *húdrōps* (ὕδρωψ), which occurs when water, *húdōr* (ὕδωρ), seeps into the tissues, that is, edema (from *oídēma*, οἴδημα, meaning "swelling"), or into a body cavity (abdominal dropsy), and he certainly appreciated the fatal prognostic implications of the latter. For, as the Father of Medicine observed in one of his aphorisms (VII:55), "When the liver is filled with water and bursts into the epiplöon, i.e., the omentum – (from *epiploon* ἐπίπλοον, meaning *to float* as it does in the abdominal cavity) – the belly is filled with water and the patient dies."[5]

Dropsy, abbreviated from the Middle English/Old French *droposie/hydropsie*, appeared in English in the late 13th century. *Aschytes*, that is, abdominal dropsy, came on the scene a century later, from the Latin *ascites* that was also originally Greek (*askites* [ασκίτης]) and literally meant "bag-like dropsy," from *askós* (ἀσκός), a leather bag or sheepskin ("wineskin") used for carrying wine, water, and oil. Cited cautiously by Hippocrates as an acceptable means of treating ascites was the use of abdominal paracentesis (*koiliakí parakéntisi*, κοιλιακή παρακέντηση),[6] which in Greek translates as a "pierce at the side," whereby the peritoneal cavity is punctured. Paracentesis in the literal sense referred to a lateral abdominal approach, yet it seems that puncture via the umbilicus (Fig. 2) was, for the longest while, the preferred route. The ideal site to puncture the abdomen, however, was a longstanding topic for debate in which the lower abdomen became most favored, either on the right near the liver or on the left (Fig. 3), and even via the scrotum when ascites had entered an inguinoscrotal hernia.[7]

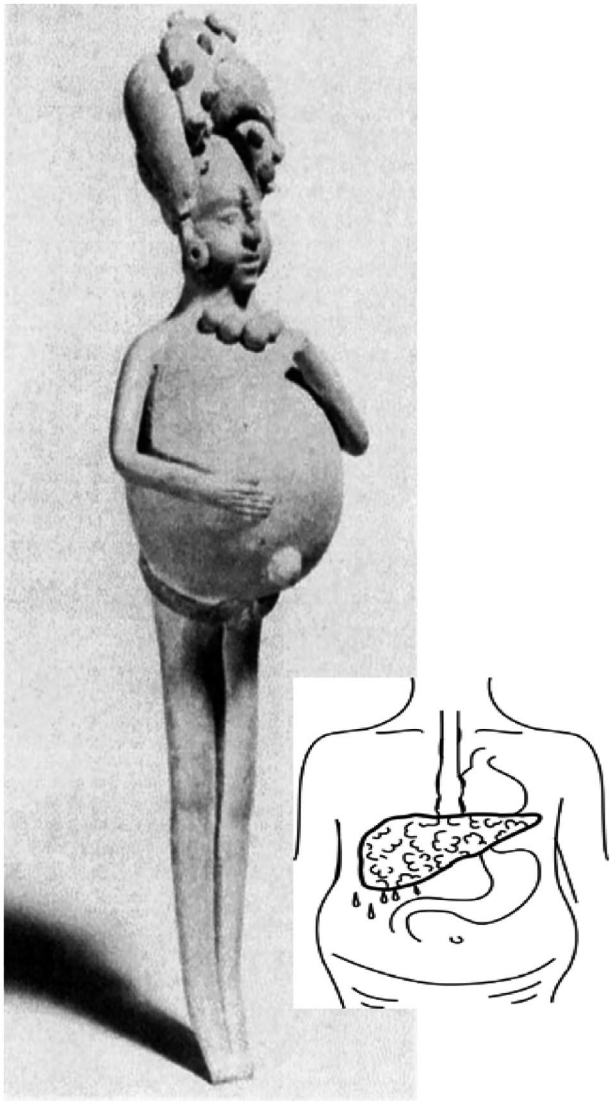

FIG 1 Hollow figurine found at the necropolis of Jaina, Mexico, depicting a man with massive ascites and an everted umbilicus. Reproduced with permission from *Annals of Internal Medicine*.[4] Copyright 1994, American College of Physicians. Inset: Hand-drawn cartoon illustrating fluid leaking into the peritoneal cavity from a "hardened" (cirrhotic) liver.

Hippocrates cautioned against too aggressive and rapid drainage,[6] as did Erasistratus of Cappadocia (325-250 BCE), the renowned third/fourth-century BCE physiologist and physician.[8] Erasistratus knew about the potential problems of overaggressive paracentesis, and therefore suggested monitoring the patient's pulse during the procedure, which should be aborted if the pulse weakens (Fig. 4). There is well-documented

* Hippocrates of Kos, Ἱπποκράτης ὁ Κῷος, from the island in the Greek Dodecanese chain in the Ægian Sea.

FIG 2 Paracentesis via the umbilicus in an engraving from Scultetus "Armamentarium chirurgicum" Lugduni Batavorum 1693.

FIG 3 Paracentesis via a puncture in the left lower abdomen, as shown by Job van Meekereen in *Heel- en Geneeskonstige Aenmerkingen*. Original first edition, 1668. Facsimile edition, introduced by D. de Moulin.

evidence that the Romans performed trephination for ascites sometime before 50 CE, using a bronze or lead tube with a flanged collar, as described by Aulus Celsus.[9] Galen of Pergamon (130-210 CE), the preeminent Greek physician[†] of Rome in those years, whose reputation and

[†] From Smyrna, modern Izmir, in Anatolia.

FIG 4 Monitoring the patient's pulse during paracentesis. This cartoon is a generous gift from Prof. Vincente Arroyo, who instructed his previous resident, the late Dr. Pablo Humbert, to draw it.

teachings endured for centuries, listed several causes of dropsy, including a "hardened liver"[10,11] (Fig. 1, inset), in agreement with Hippocrates, and reluctantly with Erasistratus before him. Paul of Ægina (625-690 CE), a Byzantine Greek physician, documented in his Medical Compendium his method to puncture the peritoneal cavity[12] by the use of a special pin or needle known as a *skolopion* (from the Greek σκολόπιον, meaning a "little stake") that was borrowed from urology instruments used in relieving phimosis.[13] A trochar was inserted through the skolopion to evacuate the abdominal fluid. In 1625, the original puncture pin was replaced with an instrument imported from his studies in Padua to the Netherlands, by the Dutch surgeon Jacob Block,[14] who was one of the intense observers in Rembrandt van Rijn's 1632 painting *The Anatomy Lesson of Dr. Nicholaes Tulp*. Block's puncture pin was later modified (Fig. 5) by the Alsatian surgeon Paul Babette, who also had settled in Amsterdam.[15] This upgrade was received with worldwide acclaim thanks to the publications by the German surgeon Johannes Schultheiss, as illustrated in Amsterdam surgeon Job van Meekereen's 1668 book *Heel- en Geneeskonstige Aenmerkingen*.

Like Hippocrates, Paul also cautioned against draining excessive fluid off too rapidly because "it evacuates the vital spirit,"[12] and he too recommended monitoring the patient's pulse during the procedure. His writings became the guiding principles for the treatment of ascites. Thus

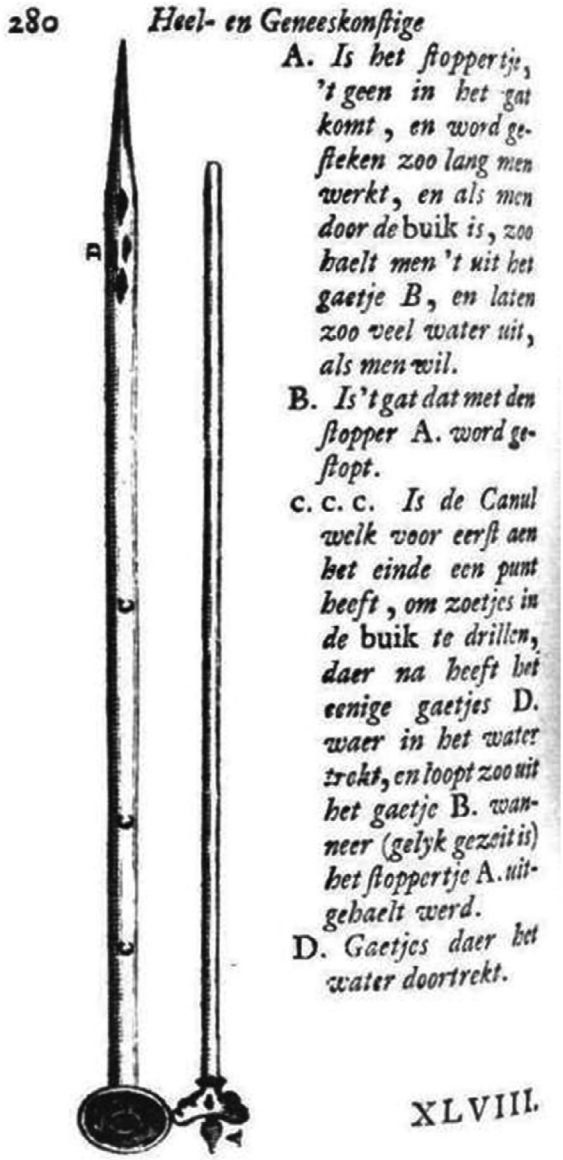

FIG 5 Modification by Paul Barbette of the puncture pin brought from Padua to Amsterdam by Jacob Block, drawn by Job van Meekereen in his book *Heel- en Geneeskonstige Aenmerkingen*, 1668.

was established abdominal paracentesis, together later with salt and water restriction, as the standard treatment of ascites for nearly 2000 years, even though there were many complications, including infection and renal failure. One famous individual who underwent repeat paracenteses was Ludwig van Beethoven (1770-1827), who enjoyed wine excessively. At his last illness that was probably terminal alcoholic cirrhosis, his massive ascites needed repeated paracentesis for symptomatic relief,[16] but ultimately he died of spontaneous bacterial peritonitis. Of note, it appears that Paget disease of bone accounted for Beethoven's deafness,[17] whereas, and yet to be substantiated, it is likely that poisoning from lead (with which wine was often adulterated in those days) could have accounted for the many abdominal symptoms that plagued him over the years.

With the advent of effective oral diuretics, paracentesis virtually disappeared for quite a while.

Head-Out Water Immersion

Ancient civilizations, including the Egyptians, Greeks, Hebrews, Chinese, and Persians, all knew about the healing effects of water, and some form of ritual washing and body immersion are features of many religions to this day.[18] The Romans built baths throughout their empire to enjoy the benefits of water immersion. Even a city in the County of Somerset in the United Kingdom was named Bath, to commemorate the presence of the Roman baths there that date from 60 to 70 CE and exist to this day. Throughout the subsequent centuries, hydrotherapy has enjoyed varying degrees of popularity (Fig. 6)[‡]. It was not until 1847, before the physiology of water immersion began to be untangled, that Hartshorne[19] reported on the presence of volume receptors in the heart that could sense the fullness of the circulation. Hartshorne's concept that water immersion caused a redistribution of the blood volume to the central compartment and thereby simulated overfilling of the circulation that would lead to a diuresis was largely ignored for more than a century. Gauer[20] reintroduced water immersion to medicine in 1965. He proposed that water immersion exerted hydrostatic pressure on the vascular columns of the body. The net effect of water immersion would be to force the blood from the lower extremities into the intrathoracic vasculature, resurrecting Hartshorne's hypothesis. Epstein and colleagues[21] used the calculation that the pressure exerted on the body increased by 22.4 mm Hg for every foot of water depth; therefore, to achieve the maximal pressure that could be exerted, it would be necessary to immerse the

[‡] These frames are from the series of satiric engravings, known as "The Comforts of Bath," by the 18th-century English caricaturist Thomas Rowlandson (published by SW Fores, London, in 1798). Rowlandson's cartoons were later used to illustrate an 1858 edition of the epistolary poem by Christopher Anstey known as "The New Bath Guide; Or, Memoirs of the B-R-D Family. In a Series of Poetical Epistles." The Guide was originally published in 1766 in the form of satirical letters written in verse by various members of a provincial family, the B-N-R-Ds or Blunderheads, who came to Bath for therapeutic reasons.

FIG 6 (A) A patient with cirrhosis with ascites and edema being attended to by his "hepatologists." From the series of satiric etchings known as "The Comforts of Bath" by the 18th-century English caricaturist Thomas Rowlandson (1757-1827), as described in a footnote to the text. (B) Bathers submerged, fully clothed, in the Roman baths in Bath. On the right, two men cling to pillars and another man is supported in the water by a servant in the foreground. The majority do not seem to enjoy the experience. Reproduced from "The Comforts of Bath" by Thomas Rowlandson. Published 1858 by W. Lewis Printer and Lithographer, 24 Union Passage, Bath.

body up to the neck to achieve maximal diuresis. They further reported that immersing the patient supine did not provide any additional diuretic effects, because the supine posture was already redistributing the blood volume from the lower part of the body to the central compartment.[22,23] The results of subsequent experiments by the same group demonstrated that the diuresis so induced was secondary to a profound natriuresis due to suppression of both the renin-angiotensin-aldosterone system and vasopressin release,[24] which act in concert to conserve sodium by the kidneys. Furthermore, the effects of head-up immersion were more pronounced in sodium-replete than in sodium-depleted patients.[24] With the introduction of effective diuretics in the latter part of the 20th century, head-out water immersion became obsolete as a means of producing a natriuresis and diuresis.

The Early Diuretics

The observation in 1920 that a patient with syphilis treated with mercurial salicylate developed a diuresis led to the development of organic mercurial diuretics and their introduction for the treatment of fluid retention.[25] However, mercury toxicity limited their use. In 1806, during his research on grape and other alternative sugars, Joseph Louis Proust, a pharmacist and chemist in Revolutionary and Napoleonic France, a nonballooning collaborator of the Montgolfier brothers, and protégé of King Charles IV of Spain, isolated the osmotic diuretic and laxative Mannitol from the sweet sap of the Fraxinus ornus, that is, the Southern European Flowering ash or Manna Ash tree[26] (Fig. 7). But like caffeine and other xanthine derivatives that were known to have mild diuretic actions, mannitol was ineffective and impractical for the treatment of ascites.

Sodium Restriction

Henry Schroeder[27] published his seminal findings in 1941 that restriction of salt intake to below that excreted in the urine would result in disappearance of edema in patients with congestive heart failure. He advocated restricting salt intake to less than 1 g/day, as the salt content in a "no-added salt" diet was not low enough to achieve negative sodium balance. He further reported that water restriction was not necessary when salt restriction was implemented, because the volume of fluid consumed did not affect the extent of edema. These same findings are still applicable to patients with fluid retention today, including patients with cirrhosis and ascites. This need to void more sodium than consumed in a palatable diet also led the pharmaceutical industry to begin developing drugs that could increase the renal excretion of sodium.

Pharmaceutical Development of Diuretics

With the synthesis of chlorothiazide by Karl H. Beyer and the elucidation of its action in inhibiting the Na^+-Cl^- cotransporter in the distal convoluted tubule, the first successful thiazide oral diuretic was launched.[28] However, thiazides were only moderately effective in relieving ascites when used as solitary agents. In contrast,

FIG 7 The Manna Ash or Southern European Flowering Ash, Fraxinus ornus. Sap (from which a sugary extract may be derived), is obtained by making a cut in the bark. This sugary extract was compared in late medieval times (around 1400 CE) with the biblical manna, giving rise to the English name of the tree, and some of the vernacular names from its native area (e.g., *fresno del maná* in Spanish and *frassino da manna* in Italian). The sugar mannose and the sugar alcohol mannitol both derive their names from the extract. Photo was taken by Jean-Pol Grandmont, CC BY 3.0: https://creativecommons.org/licenses/by-sa/3.0/. Text: Wikipedia, CC BY 3.0.

furosemide, introduced in 1963 by Kleinfelder[29] and an inhibitor of the luminal Na^+-K^+-Cl^- cotransporter in the thick ascending limb of the loop of Henle, bound Cl^- transport channels and resulted in Na^+, K^+, and Cl^- loss. Furosemide was soon confirmed by Hutcheon[30] to be an extremely effective diuretic, given orally or intravenously, but side effects such as intravascular volume depletion and electrolyte imbalance, including hypokalemia, could easily result. Therefore, furosemide had/has to be used with great caution.

The elucidation of the mechanism of renin activation at the turn of the 19th century,[31] followed by the discovery of aldosterone by Simpson and Tait[32] in 1953 and of angiotensin by scientists both in Argentina and the United States,[33] led to the recognition that the renin-angiotensin-aldosterone system plays a major role in the pathophysiology of fluid retention. Further, the realization that patients with cirrhosis with ascites have hyperreninism and hyperaldosteronism provided the rationale for eventually developing the aldosterone antagonist, potassium-sparing diuretic spironolactone in 1959,[34,35] which was approved by the US Food and Drug Administration in 1960. Blocking aldosterone receptors primarily in the proximal part of the collecting duct leads to a moderate Na^+, Cl^- diuresis while maintaining normokalemia. The combination therapy of aldosterone with conservative doses of furosemide still provides physicians with a comparatively safe diuretic regimen for long-term outpatient use in patients with cirrhosis with ascites.

The Return of Abdominal Paracentesis

The disadvantages of using diuretics were their deleterious side effects and the fact that many patients were relatively resistant to their action. Such diuretic-resistant patients had to be hospitalized for long periods on bed rest and severe salt restriction, with great inconvenience to the patient and great costs to the hospital, patient, and health care system. Therefore, in 1987, the Barcelona group performed a game-changing randomized controlled trial of oral diuretics versus carefully repeated 5-L paracentesis with albumin infusion to prevent volume depletion.[36] The study results showed convincingly that paracentesis resulted in significantly shorter inpatient stays and fewer side effects than with diuretics. The same group in Catalonia then went on to demonstrate that *total* paracentesis performed in the same careful way together with albumin infusion was without complications and even more effective than repeated modest volume drainage.[37] Variations of this therapy, with or without albumin infusion, which can be successfully performed for outpatients long term, and with minimal complications, have now become one of the standard-of-care procedures in patients with resistant ascites.

Transjugular Intrahepatic Portal-Systemic Shunts

Repeat paracentesis, even large volume, is still very inconvenient for patients, who have to attend day-care units several times a month, and is labor intensive for the physicians. Colapinto et al.,[38,39] in Toronto, Canada,

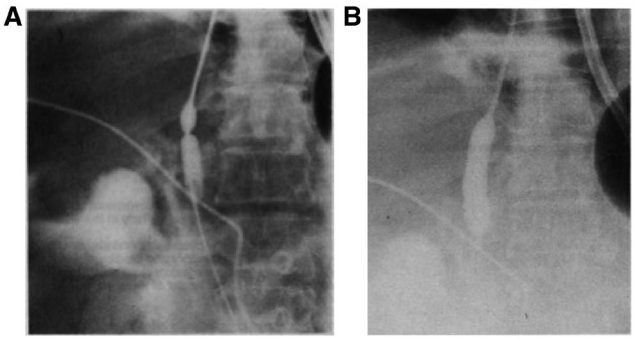

FIG 8 The creation of an intrahepatic portosystemic tissue shunt for a patient with bleeding esophageal varices. (A) A Grüntzig catheter within the tissue tract joining a branch of the portal vein with a branch of the hepatic vein, with its balloon partially inflated; therefore, a ringlike stricture is present. The tip of the catheter is in the portal vein. (B) Balloon fully dilated within the tissue tract, and hence disappearance of the constriction. Reproduced from *Canadian Medical Association Journal*.[38] Copyright 1982, Canadian Medical Association. CC BY-NC-ND.

successfully created the first venous intrahepatic tissue shunt between the middle hepatic vein and the left portal vein, as a means of reducing portal pressure in a patient with cirrhosis with bleeding varices (Fig. 8). It was soon realized that these crude tissue shunts readily collapsed and closed, and therefore stents of the kind that were used in the bile ducts were placed in the tissue tract to maintain patency. Then came the observation that patients had significant improvement in their concomitant ascites after receiving such a transjugular intrahepatic portosystemic stent shunt (TIPS). Now, several randomized controlled trials later, TIPS has been proved to be superior to repeat large-volume paracentesis in terms of ascites control for patients with refractory ascites.[40] The reduction or normalization of portal pressure achieved with TIPS results in a diuresis and natriuresis in the absence of diuretics, with the subsequent disappearance of ascites. The hydrostatic mechanism underlying this satisfying improvement combines normalization of the renin-aldosterone axis and improvement of renal function with diuresis and natriuresis.[41] In well-selected patients, the use of TIPS can also improve survival.[42] With the latest refinements in *covered* stents (by which is meant "lining" with polytetrafluoroethylene of titanium or other metal stents), TIPS insertion has become standard therapy for patients with refractory ascites, yet relatively well-preserved liver function. Efforts are now afoot to establish TIPS as a treatment option at an earlier stage in the natural history of ascites.[43]

Liver Transplantation

Thomas Starzl[44] performed the first successful human liver transplant in 1967. Since then, liver transplantation has become the standard of care for patients with severe liver dysfunction as long as there are no contraindications. Despite the fact that the development of resistant ascites in patients with cirrhosis reduces their prognosis to a 50% mortality rate within 2 years, the presence of ascites without liver dysfunction is not a sufficient indication, of itself, for liver transplantation, especially with the current Model for End-stage Liver Disease (MELD)-based organ allocation system[45] (see forthcoming essay in this series by Mousa and Kamath entitled "A History of the Assessment of Liver Performance"). The presence of refractory ascites translates into a wait-time mortality equivalent to a MELD score of 4.5 points.[46] Notwithstanding, ascites is an indication for referral to a transplant unit. Once performed successfully and in the absence of severe postoperative renal dysfunction, liver transplantation usually results in the disappearance of ascites and improvement in renal function.

HEPATORENAL SYNDROME

Friedrich Frerichs[47] and Austin Flint[48] were the first to independently describe an association between advanced liver disease, ascites, oliguric renal failure, and an absence of significant renal pathology. In 1932, Helvig and Schutz[49] introduced the term "a liver and kidney syndrome" after observing significant renal impairment after biliary surgery. In 1956, Hecker and Sherlock,[50] working at the Postgraduate Medical School of London,[§] confirmed the findings reported by Frerichs and Flint some 90 years earlier, and proposed that the most important pathophysiological change that underlies the *functional* renal failure of advanced liver disease is peripheral arterial vasodilatation. They further observed that the administration of noradrenaline (norepinephrine) and volume expansion temporarily improved renal function. In 1959, Papper et al.[51] reported intense renal vasoconstriction in otherwise normal kidneys in such patients. Vesin[52] coined the mechanistic term "functional renal failure" and noted that the disease was often terminal. The *functional* term started to be replaced in the literature[53] by the *etiological* designation "hepatorenal syndrome" (HRS).

[§] In 1974, after receiving a Royal Charter, it was renamed the Royal Postgraduate Medical School.

Early Reports of Pathogenesis of HRS

In the 1960s, the pathogenesis of this elusive *functional*, as opposed to *structural*, form of renal failure began to be elucidated. Baldus and colleagues,[54] working at Mayo Clinic in Rochester, Minnesota, using renal vein catheterization, reported that the resistance to renal blood flow was inappropriately high, and they postulated that spasm in the preglomerular arterioles reducing glomerular perfusion could be a plausible mechanism. In 1970, Epstein and colleagues,[55] using renal angiography in a patient with cirrhosis dying of renal failure, confirmed the presence of renal vasoconstriction, as suggested by Papper et al.[51] and alluded to by Baldus et al.[54] The Boston group also demonstrated postmortem filling of all renal vessels to the periphery of the cortex, thus establishing the "functional nature" of renal failure in advanced cirrhosis (Fig. 9). These now-classic premortem and postmortem renal angiographic images became the standard teaching material on HRS for the next few decades. This concurred with the clinical finding that when the kidneys from patients with renal and liver failure were transplanted into recipients with end-stage renal disease but normal liver function, there was complete reversal of the renal failure.[56] A corollary to the conclusion that the kidneys are not irreparably damaged in HRS is that spontaneous recovery of HRS also had been reported.[57]

Another salient observation in the patient with advanced cirrhosis was the finding of an elevated cardiac output,[58] which was attributed to the many arteriovenous shunts in the body[59]; in this setting, a reduced systemic vascular resistance is a physiological response to the high cardiac output.

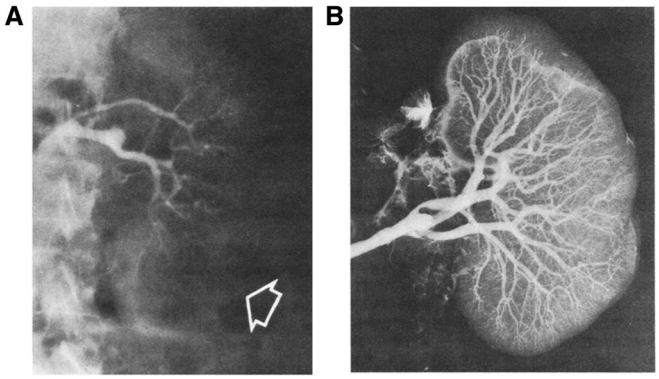

FIG 9 Selective renal angiogram performed in patient with cirrhosis and HRS. (A) Premortem showing absence of blood flow in the arcuate and cortical vessels. (B) Postmortem refilling of the renal arterial system to the periphery of the cortex in the same patient. Reproduced with permission from *The American Journal of Medicine.*[55] Copyright 1970, Elsevier.

It was further inferred that the shunting of blood from the arterial to the venous side of the circulation via these shunts was depriving the kidneys of their normal share of blood volume, leading to a reflex vasoconstrictive response. The fact that vasoconstriction reduces renal blood flow more severely in the renal cortex, where the glomeruli are located, rather than in the medulla of the kidney,[60] explains the predominant location of structural kidney injury (i.e., acute tubular necrosis) that occurs after prolonged HRS. It subsequently turned out that the pathophysiology of the circulatory changes in advanced cirrhosis was more complex than previously appreciated.[I] The combination of a high cardiac output with low peripheral resistance is the hallmark of what came to be known as the *hyperdynamic circulation*,[61-63] which is recognized clinically by the presence of warm extremities, cutaneous vascular spiders, a wide pulse pressure, and capillary pulsations in the nail beds.[58] Over time, the cellular and molecular basis of what some investigators would have preferred to call *progressive vasodilatory syndrome*, to emphasize its dynamic pathophysiology, were elucidated.[64] Early in this progressive vasodilatory state, arterial perfusion pressure is maintained by increases in cardiac output and intravascular volume, as explained so lucidly in the landmark paper on the pathophysiology of advanced cirrhosis.[65] Whereas a reflex response to systemic arterial vasodilatation is cited as the basis for the renal vasoconstriction observed in these patients,[65] dysfunction seen in other organs results directly from arterial vasodilatation in the respective vascular beds (Fig. 10).

The systemic arterial vasodilatation hypothesis was later modified when it became evident that renal perfusion is compromised when the compensatory cardiac response is no longer adequate, as depicted graphically in Fig. 11, based on data from Ruiz-del-Arbol et al.[66] Jay Cohn, who played a pivotal role in the early years of research into the hemodynamics of cirrhosis,[67] favored the cumbersome term "cardiocirculatory hepatorenal failure,"[68] which understandably did not catch on but nevertheless does summarize well the circulatory pathophysiology of portal hypertension. Acute expansion of the blood volume temporarily improves renal blood flow, despite the presence of an already elevated plasma volume.[69] The concept emerged, therefore, of a reduction in the *effective* plasma

[I] In his essay, "Portal Hypertension and Cirrhosis: From Evolving Concepts to Better Therapies," in this online series (*Clinical Liver Disease [Hoboken]* 2020;15[suppl 1]:S8-S12), Jaume Bosch succinctly develops a timeline for the evolution of the pathogenesis of portal hypertension, with an emphasis on intrahepatic events at the cellular and molecular levels.

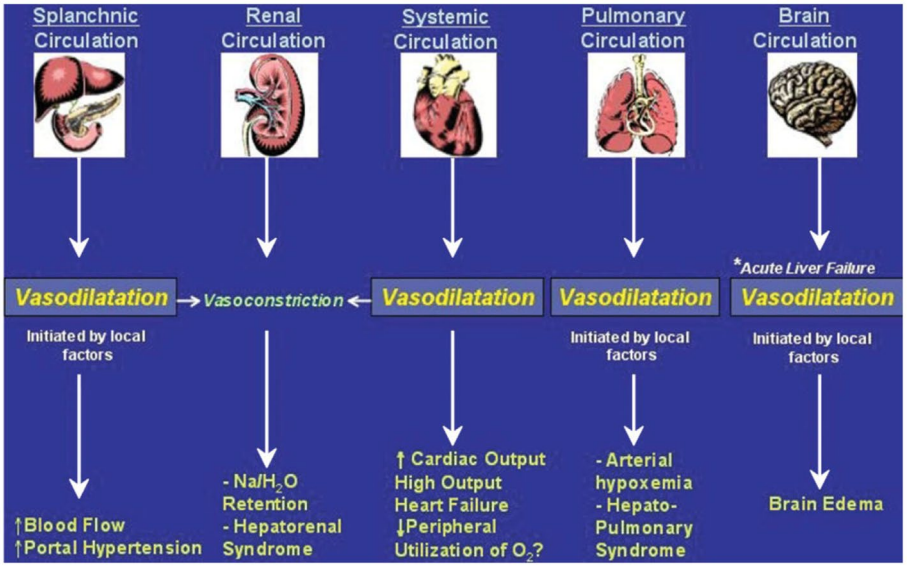

FIG 10 Diagram showing increases in active arterial perfusion in the splanchnic and pulmonary circulations, a passive increase in cerebral perfusion in acute liver failure and reflex renal arterial vasoconstriction, in association with the systemic arterial vasodilatation of advanced liver disease. Reproduced with permission from *Hepatology*.[64] Copyright 2006, American Association for the Study of Liver Diseases.

volume. Iwatsuki et al.[70] provided supportive evidence for the functional nature of the renal failure in HRS, when they reported the return of normal renal function in three patients with cirrhosis with liver and HRS-associated renal failure within 2 weeks of successful liver transplantation.

Defining "Hepatorenal Syndrome"

Although many investigators were clarifying the pathogenesis of the renal dysfunction in advanced cirrhosis, there was still a great deal of confusion as to what this condition really was. The term HRS had continued to be used since the 1930s in many sundry contexts, including the renal disease associated with biliary tract disease, liver trauma, and liver metastases. Others used the term HRS to describe renal failure induced by diuretics or other drugs, while others still used the term to describe diverse renal-related abnormalities, such as sodium retention without the presence of renal failure. Finally, purists reserved the term HRS for the renal failure observed in terminal liver failure.[71] In 1979, a group of international investigators decided to define HRS specifically as a progressive form of renal dysfunction that occurred in cirrhosis and other severe parenchymal liver diseases, with features of prerenal renal failure, but without any improvement after volume expansion.[72] These investigators also recognized that when functional renal failure was prolonged, there could be progression to acute tubular necrosis. Yet, as long as there were no diagnostic criteria for functional renal failure, there continued to be confusion over what truly constituted HRS. This led to an editorial in the *Lancet*[71] that proposed the unintuitive term "hepatic nephropathy" to distinguish functional renal failure from any combination of renal failure occurring with liver failure, such as acetaminophen overdose causing combined liver and kidney injury/failure, or acute glomerulonephritis in a patient with advanced liver disease.

With the publication of the memorable peripheral vasodilation hypothesis paper in 1988,[65] the hepatology community was ready to work together to further delineate renal dysfunction in cirrhosis. Therefore, in 1990, a group of experts with an interest in the complications of portal hypertension joined together to form the International Ascites Club (IAC). These were hepatologists who had an in-depth understanding of kidney physiology, hemodynamics, electrolyte disorders, infections, cardiopulmonary function, and transplant medicine. The goals of the club were to stimulate discussions and research in ascites and related topics. In 1996, the IAC renamed hepatic nephropathy as HRS, defined as a syndrome that occurs in patients with cirrhosis, portal hypertension, and advanced liver failure, characterized by impaired renal function with marked abnormalities in the arterial circulation and activity

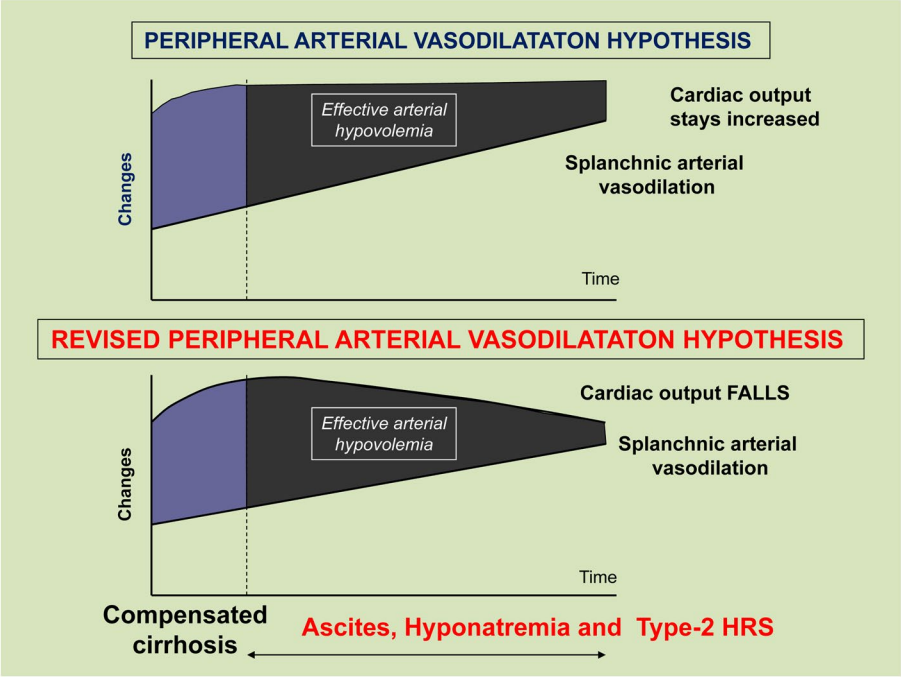

FIG 11 Schematic depiction of the changes in cardiac output with a progressive increase in systemic arterial vasodilatation, as exemplified by splanchnic vasodilatation. The upper panel shows the change in hemodynamics according to the original peripheral vasodilatation hypothesis, in which cardiac output increases to a plateau. The lower panel shows that cardiac output rises to a peak with increasing splanchnic vasodilatation only to fall thereafter, which explains the impaired renal function that is seen with the most advanced portal hypertension. Reproduced with permission from *Seminars in Liver Disease*.[74] Copyright 2008, Thieme Medical and Scientific Publishers Private Limited.

of endogenous vasoactive systems.[73] Clinically, HRS was divided into two types. Type 1, or HRS1, is an acute form that occurs in the setting of multiorgan failure[74] and is characterized by a rapidly progressive reduction of renal function, defined as a doubling of the initial serum creatinine (sCr) to >220 µmol/L (2.5 mg/dL) or a 50% reduction of the initial 24-hour creatinine clearance to <20 mL/min in less than 2 weeks. Type 2, or chronic HRS (HRS2), was defined as moderate *functional* renal failure that progressed gradually over weeks to months, with a sCr between 133 and 220 µmol/L (1.5-2.5 mg/dL).

Further Refinements in the Definition of HRS

In 2005, during the tenure of Paolo Angeli as Secretary, the IAC changed its name to the International Club of Ascites (ICA), a move that had been decided previously when Francesco Salerno was Secretary. The purpose of rearranging the three-word title might have been assumed to clarify that it was the club that was "international" and not the ascites. In fact, however, the reason for the rearrangement was a devilish attempt to summarize important foci of interest for the club, based on the contrived acronym ASCITES that stood for Ascites, Spontaneous bacterial peritonitis, Cardiac involvement, Therapy, and End-Stage disease or maybe Extracorporeal Support. The official name change has persisted, but the acronym is all but blessedly forgotten. In 2007, the ICA (the IAC that was) updated the definition and diagnostic criteria for HRS.[75] This came about because of improved understanding of the pathophysiology of HRS, especially with the recognition that HRS1 frequently follows bacterial infections and, in particular, spontaneous bacterial peritonitis. The updated diagnostic criteria allowed patients with renal failure after a bacterial infection to be identified as having HRS, permitting treatment of infected patients with the newer effective vasoconstrictors and thereby improving their survival. It was also recognized that HRS was no longer necessarily a fatal condition, even if liver transplantation was not performed.

Starting from the 2000s, the nephrology community started using a dynamic change rather than a static level of sCr to describe renal dysfunction, because they found

that this could overcome some of the shortcomings of using sCr as a biomarker of the condition. The term "acute kidney injury" (AKI) was coined, which is defined as an acute increase in sCr of 26.4 µmol/L (0.3 mg/dL) in less than 48 hours. Such a small change in sCr has been shown to have a negative impact on patient outcomes in populations without cirrhosis. The ICA also adapted the term AKI to describe acute renal dysfunction in cirrhosis. HRS1 then became a special form of AKI, which was renamed appropriately AKI-HRS, in which sCr had to double in value with the acute change presumably having occurred within the previous 7 days,[76] when all other causes of renal dysfunction have been excluded. This latest definition has the advantage of allowing treatment for HRS to begin before a static threshold of sCr of 222 µmol/L (2.5 mg/dL) is reached. Such a level of sCr could underrepresent serious renal dysfunction that is underestimated in patients with cachexia with end-stage liver disease, because sCr is often artefactually "low" because the source of creatinine, namely, muscle creatine, is diminished by sarcopenia. Over the past few years, there have been many studies that have confirmed that AKI as defined can accurately predict outcomes in the population with cirrhosis. The future of HRS will center on finding appropriate treatment options to reduce the likelihood of a fatal outcome.

SERIES EDITOR'S POSTSCRIPT

It seems that the Dominion of Canada (the name derived from the St. Lawrence Iroquoian word for a "village" or "settlement") attracts world-class hepatologists, in whose pedigree is the gene for migration. The current pair of peripatetic prestigious authors, like two others before them (Mina Niazi from Saskatoon, Saskatchewan, and Juan Abraldes from Edmonton, Alberta: "Can We Add the History of the Nonoperative Therapy of Varices to Other Success Chapters of Modern Medicine?" *Clinical Liver Disease [Hoboken]* 2020;16[suppl 1]:73-82), certainly deserve that appellation. And I expect that we will see more in future essays.

Florence Wong was born in Hong Kong, whither her parents-to-be had migrated away from the turmoil in mainland China, where a bitter civil war had raged after WWII. When the opportunity arose, her parents, who had an extensive paternal sheep-farming family near Auckland, New Zealand, and a large maternal family (early gold prospectors) in Melbourne, Australia, migrated in stages to Melbourne, with their four children. Florence therefore received her education in Australia. However, a serendipitous encounter at an Australian meeting with Laurie Blendis, who was chairing a session at which she had successfully presented a 10-minute oral paper, led to the next migration, to Toronto. And, as the saying goes,[¶] the rest is history.

Laurie Blendis himself has been far from sedentary. He was born in London, of parents whose families had migrated to the United Kingdom from Vilna and Poland, respectively, in the decades before and after the turn of the 20th century. In Laurie, the Blendis migration gene was active, too, as he left his birthplace to settle, for a while, in a "Place of plenty, where the trees stand in the water," that is, in *tkaronto*, the original Iroquoian name for the modern-day gleaming multicultural metropolis of Toronto. Whereas that might have satisfied a less restless individual, Laurie then pursued his dream of going up to the ancient city of Jerusalem, from where he commuted monthly for quite a while, to and from Toronto, but now where he and Maxine reside permanently. The roving gene has downregulated at last.

The current duplex essay that links the related topics of ascites and HRS has an emphasis on the Greek origins of the many medical terms used and the complex shared common pathophysiology. The authors' consummate knowledge of and indeed personal involvement in the history of these two major topics in hepatology provides for the reader a worthy guide for what otherwise would be a tortuous journey. Seemingly, their navigational skills in topography also ably play a pivotal role in their scientific work, to which the current essay attests.

CORRESPONDENCE

Florence Wong, Department of Medicine, Division of Gastroenterology, University of Toronto, Room 222, Eaton Wing, Toronto General Hospital, 200 Elizabeth Street, Toronto, ON M5G2C4, Canada. E-mail: florence.wong@utoronto.ca

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